REMARKS

Claims 1-31 are pending and claims 1-5 and 20 are been rejected in the above-identified application. Claims 6-19 and 21-31 are withdrawn from further examination by the Examiner.

Support for all amendments are found in the originally filed specification and claims. No new matter has been added to the claims or specification by amendment.

Applicants' Attorney Grace Hsu wishes to thank Supervisory Examiner Joesph McKane, Primary Examiner Celia Chang and Examiner Andrew Freistein for the in-person interview/discussion of issues of the outstanding August 2, 2006 Office Action at the January 29, 2007 Interview conducted at the U.S. Patent Office.

This Amendment is filed in response to the August 2, 2006 Office Action and in light of the aforementioned Examiners' Interview discussion.

Applicants request consideration and entry into the record of the following amendments and remarks.

Restriction Requirement

The Examiner has acknowledged applicants' provisional election, with traverse, to prosecute:

Group I: Claims 1-5 and 20, drawn to the compound carvedilol dihydrogen phosphate hemihydrate and a pharmaceutical composition, which comprises carvedilol dihydrogen phosphate hemihydrate

Despite applicants' traversal arguments and the fact that the Examiner admits in the August 2, 2006 Office Action that he erred in citing an incorrect unity breaking reference directed to non-relevant subject matter (i.e., U.S. Pat. No. 4,053,067 to Katz et al. directed to "Fuel Transfer System to a Nuclear Reactor"), the Examiner has maintained and made final the June 7, 2006 restriction requirement and also withdrawn corresponding method claims as being drawn to non-elected subject matter.

The Examiner states that:

> "Examiner agrees with Applicant because this was a typographical error. . . Although Examiner mistakenly cited the wrong reference, the concept is the same . . . Applicant further traverses the restriction requirement , because there is no search burden. Examiner did not allege in the previoys Office Action that a search burden exists, but rather a "serious burden" exists as a result of the lack of unity of invention . . ."

In light of the foregoing, applicants' July 7, 2006 response arguments are reiterated herein in there entirety, excerpts of which are set forth below.

> "Under M.P.E.P. 808.02, "the Examiner in order to establish reasons for insisting upon restriction, must explain why there would be a serious burden on the examiner

if restriction is not required. Thus the examiner must show by appropriate explanation one of the following:

(A) **Separate classification thereof**: . .
(B) **A separate status in the art when they are classifiable together**. . ..
(C) **A different field of search . . .**

Where, however, the classification is the same and the field of search is the same and there is no clear indication of separate future classification and field of search, no reasons exist for dividing among independent or related inventions."

If the search and examination of all the claims in an application can be made without serious burden, the examiner must examine them on the merits, even though they include claims to independent or distinct inventions."

In light of the above, applicants respectfully maintain that Examiner has not provided sufficient evidence or reasons to establish why restriction is proper or to show why a serious search burden would be imposed upon examination of the claimed invention for the following reasons.

the reference cited to break unity of invention, U.S. 4,053,067 to Katz et al. is directed to a "Fuel Transfer System to a Nuclear Reactor" and is not related to carvedilol salts, anhydrates or solvates of the above-identified application;

the Examiner stated that "compounds of Group I-IX of claimed invention are drawn to the common structural moiety carvedilol", and

no assignment of individual class and subclasses designations from the U.S. Classification Manual to the Groups I-IX, respectively.

Further, applicants also wish to reiterate the request herein that as the elected subject matter for examination on the merits is directed to a product, rejoinder of commensurate in scope non-elected subject matter or inventions (i.e., such as methods or processes) upon the determination of allowable subject matter (*In re Ochiai*, 71 F.3d 1565, 37 USPQ2d 1127 (Fed. Cir. 1995) and *In re Brouwer*, 77 F.3d 422, 37 USPQ2d 1663 (Fed. Cir. 1996); also see MPEP § 821.04 (b)).

Applicants reserve the right to file non-elected inventions as the subject of future applications, which may derive priority from the present application, without prejudice.

In addition, applicants respectfully believe that it is improper for an Examiner to make final a restriction requirement in light of his admitted error in citing an incorrect reference in regard to unity of invention issues.

Based upon the above, applicants respectfully request reconsideration and that the Examiner withdraw the finality associated with and in addition to withdrawal of the above-identified restriction requirement.

Rejection Under 35 U.S.C. §112, 1st paragraph

Claims 1-5 and 20 are rejected under 35 U.S.C. §112, 1st para., for failure to comply with the written description requirement as the claims contain subject matter not described in the specification to reasonably convey that the inventors has possession of the claimed invention at the time the application was filed.

The Examiner states that pending claims 1-5 are directed to "A compound which is carvedilol dihydrogen phosphate hemihydrate." The Examiner asserts that applicants' deletion of the term "crystalline" from original claim 1 in the December 16, 2004 Preliminary Amendment represents new matter and "an attempt to broaden the scope of the claims from a crystalline form to include all forms of the compound carvedilol dihydrogen phosphate hemihydrate". The Examiner also states Example I of the specification identifies a crystalline form of carvedilol dihydrogen phosphate hemihydrate as Form I and U.S. Prov. Appln. 60/392, 175 identified a crystalline Form as Example 1

To advance prosecution, applicants have amended pending claim 1 to include the term "crystalline" to overcome the above-identified rejection.

In light of the above amendments, applicants request that the above rejection under 35 U.S.C. § 112, 1st paragraph, be withdrawn.

Rejection Under 35 U.S.C. §103(a)

Claims 1-5 and 20 are rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 4,503,067 to Wiedemann ("Wiedemann "; Filed: April 4, 1983, Issued: March 5, 1985) and U.S. Patent No. 6,699,997 to Hildesheim ("Hildesheim"; Filed: June 28, 2001, Issued: March 2, 2004).

The Examiner states that:

> Wiedemann "disclose and claim the compound of carvedilol and the salts thereof with physiologically acceptable acids"; and
>
> Hildesheim disclose "that the term "carvedilol" includes hydrates and solvates of carvedilol and the hydrate and solvate forms are only distinct from on another in their powder X-ray diffraction patterns and their thermal profiles" and "polymorphs of carvedilol".

Further, the Examiner states that "one of skill in the art would have been motivated to prepare different salt forms of known pharmaceutically useful benefit, such as longer shelf like, stability, enhanced deliverability, etc. Therefore, absent a showing of unobvious and superior properties, the instant claimed salt or crystalline forms of known compounds would have been suggested to one skilled in the art" as " . . . changing the form, purity or other characteristic of an old product without a new use as a result thereof does not render product patentable where utility remains the same (Ex parte Hartop)" and " . . . changing the

form, purity or other characteristic of an old product does not render the novel form patentable where the difference in form, purity or characteristic was inherent in or rendered obvious by the prior art (In re Cofer)" and "

Applicants respectfully traverse the above-identified rejection.

According to the M.P.E.P Section 2142, to establish a case of prima facie obviousness, three basic criteria must be met:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings.
>
> Second, there must be a reasonable expectation of success.
>
> Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

In general, the present invention teaches salt, anhydrate or solvate forms of carvedilol phosphate, corresponding compositions containing and treatment methods using the aforementioned forms for specific cardiovascular diseases.

The present invention relates to a compound, which is a salt and/or novel crystalline forms of carvedilol phosphate (i.e., which include crystalline forms of carvedilol dihydrogen phosphate, carvedilol hydrogen phosphate, etc.) and/or solvates of carvedilol phosphate (i.e., which include carvedilol dihydrogen phosphate hemihydrate, carvedilol dihydrogen phosphate dihydrate (i.e., such as Forms II and IV, respectively, etc.), and/or carvedilol dihydrogen phosphate methanol solvate, etc.). Examples in the specification are directed to the following compounds: carvedilol dihydrogen phosphate hemihydrate (Form I), carvedilol dihydrogen phosphate dihydrate (Form II), carvedilol dihydrogen phosphate methanol solvate (Form III), carvedilol dihydrogen phosphate dihydrate (Form IV), carvedilol dihydrogen Phosphate (Form V) and carvedilol hydrogen phosphate (Form VI).

Applicants respectfully submit that Wiedemann and Hildesheim, respectively alone or in combination, fail to support a *prima facie* case of obviousness as the aforementioned references do not provide any suggestion or motivation to try to make the specific carvedilol phosphate salts, anhydrates or solvates thereof of the present invention or what would be the requisite expectation of success in obtaining the claimed carvedilol phosphate forms of the present invention.

Wiedemann generally teaches a generic carbazolyl-(4)-oxypropanolamine compound

of the formula as defined therein and pharmaceutically acceptable salts thereof.

While Wiedemann specifically discloses the free base form of carvedilol (i.e., 1-[carbazolyl-(4)-oxy]-3-[2-(2-methoxyphyenoxy)-ethylamino]-propan-2-ol; see Example 2 at col. 5, lines 54-68 to col. 6, lines 1-30) and hydrochloride salts associated with other carbazolyl-(4)-oxypropanolamine compounds (see Example 6, col. 10, lines 51-68, Examples 7-8, col. 11, lines 1-68), Wiedemann does not disclose salts, solvates or anhydrates of carvedilol (i.e., 1-[carbazolyl-(4)-oxy]-3-[2-(2-methoxyphyenoxy)-ethylamino]-propan-2-ol).

Moreover, Wiedemann does not teach any specific carvedilol phosphate salts, anhydrate or solvate forms thereof as disclosed in the present invention.

Wiedemann provides no disclosure as to how to obtain or make any one of the carvedilol phosphate salts, anhydrate or solvate form derivatives or pharmaceutical compositions containing those derivatives of the present invention.

Hildesheim teaches a process for preparing carvedilol and in particular a carvedilol hydrochloride hydrate form, defined as "a crystalline material having a water content of about or above 2% w/w (see col. 5, lines 13-15)".

More importantly, Hildesheim provides only disclosure with regard to carvedilol hydrochloride, but provides no disclosure as to how to obtain any one or more of the carvedilol phosphate forms of the present invention.

In contrast, the carvedilol phosphate salt, solvate, anhydrate, polymorphic forms of the present invention are different from carvedilol hydrochloride polymorphic forms as taught by Hildesheim.

Further distinguished from Wiedemann and Hildesheim, the present invention relates to a novel salt, anhydrate or solvate form of carvedilol phosphate "with greater aqueous solubility, chemical stability, etc. offering many potential benefits for provision of medicinal products containing the drug carvedilol, but further include the ability of polymorphs of the present invention to achieve desired or prolonged drug levels in a systemic system by sustaining absorption along the gastro-intestinal tract of mammals (i.e., such as humans), particularly in regions of neutral pH, where a drug, such as carvedilol, has minimal solubility (see specification at page 2, lines 22-30)". The specification further states that "Surprisingly, it has now been shown that a novel crystalline form of carvedilol phosphate salt (i.e., such as carvedilol dihydrogen phosphate and/or carvedilol hydrogen phosphate, etc.) can be isolated as a pure, crystalline solid, which exhibits much higher aqueous solubility than the corresponding free base or other prepared crystalline salts of carvedilol, such as the hydrochloride salt. This novel crystalline form also has potential to improve the stability of carvedilol in formulations due to the fact that the secondary amine functional group attached

to the carvedilol core structure, a moiety pivotal to degradation processes, is protonated as a salt (see specification at page 2, lines 32 to page 3, lines 1-8).

Applicants maintain that the compounds of the present invention are "not old products" with "changed forms with a new use" as suggested in Ex Parte Hartop (139 USPQ 525) as noted by the Examiner. Because one of ordinary skill in the art would generally understand that "polymorphism is the property of some molecules and molecular complexes to assume more than one crystalline form in the solid state [and] that a single molecule may give rise to a variety of crystal forms (also called "polymorphs", "hydrates" or solvates") having distinct physical properties" as taught by Hildesheim (see col. 2, lines 50-60)

In light of this, the conventional chemical literature supports the novelty and unobviousness of polymorphic forms of the present invention by teaching that each polymorphic form is chemically unique, distinct and different from other polymorphic forms, i.e., representing a different chemical compound as each form has unique and differentiable physical and chemical differences/properties from other polymorphic form(s), which are quantitatively and physically identified by spectroscopic/other characterizing data/spectrum means (i.e., IR, X-Ray data, etc.).

For example, the chemical literature teaches that:

> "Different polymorphs of a given compound are in general as different in structure and properties as the crystals of two different compounds. Solubility, melting point, density, hardness, crystal shape, optical and electrical properties, vapour pressure, stability, etc. all vary with the polymorphic forms . . ."; and that
>
> even though two polymorphs of a given compound may have identical compositions (e.g., two hydrates containing the same amount of water), the form and properties of each of these polymorphs would, in general, be different (See generally, Chemical & Engineering News, February 24, 2003, pp. 32-35; and Jain et al., "Polymorphism in Pharmacy", Indian Drugs, 23 (6), 1986, pp. 315 -329).

Moreover, the fact that Hildesheim teaches that a variety of detection techniques, such as differential scanning calorimetry, X-ray diffraction and infrared spectroscopy, can determine the existence of or differentiate between different polymorphic forms only indicates that conventional art known diagnostic identification tools are available to the skilled artisan to verify a specific compound, such as a chemically distinct polymorphic form, has been made.

However, even in light of the art, it would not be obvious how an ordinary artisan could determine which specific or different polymorphic forms of carvedilol to prepare by reaction with different acids, reagents or other solvents or varying other properties, parameters, etc., without further experimentation.

Applicants respectfully point out that obvious to try or experiment is not the standard under 35 U.S.C. § 103, where "the prior art gave no indication of which parameters were critical or no direction as to which of the possible choices is likely to be successful (see, MPEP Section 2145 (X)(B) at lines 6-12). There must be a motivation to pick, use, combine or prepare compounds with specific functional group components or conduct functional group conversions of compounds taught by the present invention by reaction with various known chemical reagents to generate derivative compounds which may be taught by another art reference. Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention absent some teaching, suggestion or incentive supporting the combination. *In re Geiger*, 2 USPQ 2d 1276 (Fed. Cir. 1987).

Absent such suggestions, there would be no reasonable reason why one skilled in the art would be motivated to prepare polymorphic forms of carvedilol phosphate taught by the present invention in view of Wiedemann's teaching of a generic carbazolyl-(4)-oxypropanolamine compound of the formula as defined therein and pharmaceutically acceptable salts thereof and the free base form of carvedilol (i.e., 1-[carbazolyl-(4)-oxy]-3-[2-(2-methoxyphyenoxy)-ethylamino]-propan-2-ol; see Example 2) and Hildesheim's teaching of carvedilol hydrochloride forms without some teaching, suggestion or incentive supporting such a product as it is well known in the art, as even Hildesheim teaches that:

> "the existence and physical properties of polymorphs, hydrates and solvates is unpredictable (see Hildesheim, col. 3, lines 4-5)".

It is improper to combine references where the references teach away from their combination. *In re Grasselli*, 713 F. 2d. 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983). The totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. *In re Hedges*, 783 F. 2d. 1038, 228 USPQ 685 (Fed. Cir. 1986).

Moreover, in view of the above, there would be no reasonable expectation of success that a carvedilol phosphate salt, anhydrate or solvate thereof would exhibit the same chemical and physical properties carvedilol hydrochloride polymorphs, hydrates and solvates taught in Hildesheim, such as solubility in aqueous solution (gastric juices of patient).

In view of the distinctions pointed out ***supra***, Wiedemann and Hildesheim, respectively, alone or in combination, does not teach or suggest all of the necessary elements which are critical or essential to form or produce the novel carvedilol phosphate forms of the present invention.

For the record, applicants note herein that the courts have addressed the patentability of polymorphs finding that new crystalline forms of old compounds are patentable and have indicated that the demonstration of "unexpected results" is not required to establish the patentability of novel crystalline forms.

The issue of patentability of novel crystalline forms has been addressed by the CCPA and the Federal Circuit Court of Appeals.

In each case, the courts have long held that new crystalline forms of old compounds are patentable and are not obvious over other forms of the old compound. *Bristol-Myers Co. v. U.S. International Trade Commission*, 15 USPQ 2d 1258 (Fed. Cir. 1989, unpublished), provides a review of decisions affirming the patentability of new crystal forms. See for example *In re Cofer*, 354 F.2d 664, 148 USPQ 268 (CCPA 1966), *In re Irani* 427 F.2d 806, 166 USPQ 24 (CCPA 1970), and *In re Grose,* 592 F.2d 116, 201 USPQ 57 (CCPA 1979).

Moreover, the courts have indicated that the demonstration of "unexpected results" is not required to establish the patentability of novel crystalline forms. The court in *Grose* specifically rejected the application of the law of structural obviousness, and hence a requirement for a showing of unobvious properties, when analyzing the patentability of novel crystalline forms.

The court in *Grose* specifically rejected the application of the law of structural obviousness, and hence a requirement for a showing of unobvious properties, when analyzing the patentability of novel crystalline forms. (M.P.E.P. 2144.02)

> No reason exists for applying the law relating to structural obviousness of those compounds which are homologs or isomers of each other to this case. When the PTO seeks to rely upon a chemical theory, in establishing a prima facie case of obviousness, it must provide evidentiary support for the existence and meaning of that theory. In re Mills, 47 CCPA 1185, 1191, 281 F.2d 218, 223-24, 126 USPQ 513, 517 (1960). The known structural relationship between adjacent homologs, for example, supplies a chemical theory upon which a prima facie case of obviousness of a compound may rest. A zeolite, like those of the instant case, is not a compound which is a homolog or isomer of another, but is a mixture of various compounds related to each other by a particular crystal structure. Moreover, no other chemical theory has been cited as a basis for considering appellants' zeolite as prima facie obvious in view of Milton's zeolite R.

In re Grose, 592 F.2d 1161,1167-1168, 201 USPQ 57,63 (CCPA 1979).

Based on the cited case law and the fact the Examiner has failed to establish a prima facie case of obviousness in the present application, applicants should not be required to submit any data showing unexpected and superior properties

In light of the foregoing, applicants respectfully maintain that a prima facie case of obviousness has not been made by Wiedemann and Hildesheim, respectively, alone or in combination.

In light of the above, applicants request that the above rejection under 35 U.S.C. §103(a) be withdrawn

Double-Patenting

Claims 1 and 20 are provisionally rejected on the ground of non-statutory obviousness-type double patenting over pending claims 2 and 34 of co-pending U.S. Patent Appln. No. 10/977,230.

Applicants respectfully point out to the Examiner that the correct serial number for the U.S. Patent Appln. No. cited in the above-identified rejection is U.S. Pat. Appln. Serial No. 10/997,230 and not U.S. Pat. Appln. Serial No. 10/977,230 ("U.S. '230 Appln.").

The Examiner points out the claims 1 and 20 of the present invention are drawn to a compound "carvedilol dihydrogen phosphate hemihydrate" and a corresponding pharmaceutical composition containing the aforementioned compound, respectively.

For clarification, claim 2 of U.S. '230 Appln. is directed to a compound which is a crystalline salt, anhydrous forms or solvate of carvedilol, which includes "carvedilol dihydrogen phosphate hemihydrate" and claim 34 is directed to a pharmaceutical composition containing the aforementioned compound(s) of claim 2.

In the interest of advancing patent prosecution, applicants have filed a Preliminary Amendment on January 30, 2007 in co-pending U.S. '230 Appln., where claim 2 in the aforementioned co-pending application is amended to delete the term "carvedilol dihydrogen phosphate hemihydrate". Dependent claim 34, now also refers to the compound(s) recited in amended claim 2.

In light of the above, applicants request that above-identified provisionally rejected non-statutory obviousness-type double patenting be withdrawn in the above-identified application.

CONCLUSION

In view of the above amendments and remarks, reconsideration of this application is requested. Applicants believe that the claims of the present application are in condition for allowance and is earnestly solicited. Applicants respectfully request that a timely Notice of Allowance be issued in the present application.

If any additional fees or charges are required authorization is hereby granted to charge any necessary fees to Deposit Account No. 19-2570 accordingly.

Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is encouraged to call the undersigned attorney at the number below.

Respectfully submitted,

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